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Factors related to successful antiepileptic drug withdrawal after anterior temporal lobectomy for medial temporal lobe epilepsy

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Summary

Objective: To assess the rate of successful antiepileptic drug (AED) discontinuation, prognostic factors and proper time of AED withdrawal after surgery for medial temporal lobe epilepsy (MTLE).
Methods: We reviewed 171 consecutive patients who underwent resective surgery for MTLE. All patients were followed up for more than two postoperative years. AEDs were slowly tapered with an individualized schedule for each patient. Outcome status was determined from medical records and telephone interviews.
Results: 41.2% of patients experienced no seizure recurrence. 34.5% discontinued medication without seizure recurrence for more than 2 years at final assessment. Multivariate analysis revealed that an age greater than 30 years at surgery and postoperative AED reduction before 10 months increased the risk of recurrence [hazard ratio (HR) 2.1, 95% confidence interval (CI) 1.1—3.9 and HR 2.5, CI 1.1—5.8].
Conclusions: Resective surgery for MTLE brings seizure remission without AED to one-third of patients. Postoperative AED tapering is recommended after at least 10 months. Younger age at surgery is a good predictive factor of remission after MTLE surgery.

Introduction

Medial temporal lobe epilepsy (MTLE) is the most common form of partial epilepsy in adults, and

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anterior temporal lobectomy is the most frequently performed epilepsy surgery. Long-term seizure-free rates after anterior temporal lobectomy for MTLE range from 55 to 80%, according to definitions used and follow-up duration.[1–4] However, little information is available regarding antiepileptic drug (AED) withdrawal after successful surgery. Successful AED discontinuation rates have been reported to range from 10 to 45%,[4–7] with different AED withdrawal policies. In medically treated epilepsy patients, a minimum 2-year seizure-free period is generally recommended before AED withdrawal.[8] We attempt withdrawal earlier in children with an epileptic syndrome known to have a favorable prognosis. On the other hand, for surgically treated epilepsy patients, no guidance is available regarding required seizure-free times before AED withdrawal. Surgically treated patients may require shorter seizure-free intervals because the epileptogenic focus was removed. In the present study, we purposed to deduce the proper timing for AED withdrawal and to elucidate the effects of presurgical laboratory findings and clinical settings on AED withdrawal outcomes, in a homogeneous group of patients who received epilepsy surgery for MTLE.

Patients

We reviewed consecutive patients who were proven to have MTLE and received anterior temporal lobectomy, including amygdalohippocampectomy, between January 1994 and April 2002. MTLE was diagnosed; (1) when hippocampal sclerosis or another definite lesion was exclusively located inside the collateral sulcus, and (2) when an anterior temporal ictal onset was identified by video-EEG monitoring. Patients with neocortical lesions or bilateral hippocampal sclerosis were excluded. Patients with critical incongruent ictal semiology or ictal EEG findings were also excluded. One hundred seventy-one patients fulfilled the inclusion criteria, and all patients were followed up for more than 2 years postoperatively. Patients were identified from a computerized database containing information on all patients those underwent epilepsy surgery at Seoul National University Comprehensive Epilepsy Center.

Data collection and neurosurgery

Clinical parameters included age at nonfebrile-seizure onset and at surgery, duration of epilepsy, seizure frequency, number of AEDs, and history of febrile convulsion.

All patients received video-EEG monitoring, brain magnetic resonance imaging (MRI) including 3 mm sections perpendicular to the long axis of the hippocampus, F-18 fluorodeoxyglucose positron emission tomography (PET), ictal and interictal single photon emission computed tomography (SPECT), if possible, and the Wada test.

All patients with hippocampal sclerosis underwent anterior temporal lobectomy to an extent of 3.5 cm for the left and 4.5 cm for the right, with amygdalohippocampectomy. Some patients with other lesions received lesionectomy with hippocampectomy and anterior temporal lobectomy of variable extent.

Gross and microscopic tissue analyses were performed in all cases. Hippocampal sclerosis was defined as >50% neuronal loss in CA1.

Clinical parameters, presurgical evaluations, i.e., the presence of hippocampal sclerosis on MRI, contralateral spikes on EEG, and contralateral localization on SPECT or PET, were considered as potential prognostic factors.

Postoperative antiepileptic medication

The policy for postoperative antiepileptic medication was maintenance of preoperative medication for more than one month, and then AEDs were slowly tapered, with an individualized schedule for each patient. We included unscheduled arbitrary AED reductions in the analysis.

Postoperative follow-up and outcome classification

Data collected included seizure recurrence, time of recurrence, and AED medication details. Surgical outcomes for 1 year at the final assessment were graded using the Engel classification; class I was divided into seizure-free with AED and seizure-free without AED. The classification "seizure-free without AED" was defined as the absence of seizure for more than 2 years without medication. Seizure outcomes for the entire follow-up period were classified as: (1) seizure free, (2) aura only, (3) seizure recurrence, and (4) reoperation. The information was collected from hospital charts and outpatient medical records and was supplemented by telephone contact for the latest follow-up.

Statistical analyses

Data were analyzed using SPSS ver. 11.0. The χ^2 test was used for categorical variables. The influences of potential predictive factors on postoperative recurrence were evaluated by univariate and multivariate Cox regression analysis. Hazard ratios (HR) are presented with 95% confidence intervals (CI). Times to seizure recurrence after initial AED reduction were plotted as a Kaplan—Meier curve.

Results

Patient characteristics

Mean age at surgery was 29.0 (9—55) years, and mean duration of epilepsy prior to surgery was 15.4 ± 8.63 (standard deviation) years. Preoperative seizure frequency was 7.51 ± 16.9 per month. Fifty-eight percent of patients had a history of febrile convulsions. All except eight (4.7%) patients had unilateral hippocampal sclerosis by MRI. Pathologically determined lesions in these eight patients were; two cavernous angiomas, three dysembryoplastic neuroepitheliomas, two gangliogliomas, and one choroid plexus papilloma (Table 1).

Seizure outcome

The mean postoperative follow-up period was 69.0 ± 28.9 months. Seventy (41.2%) patients experienced no seizure recurrence or aura throughout postoperative follow-up, and 18 (10.6%) patients experienced only aura, 80 (47.1%) patients had one or more seizure; and two (1.2%) patients underwent further operations because of frequent seizures (Fig. 1A). One patient had somniloquy-like episodes that were not identified. Final seizure outcomes for 1 year according to Engel's classification, were as follows: 124 (72.5%) patients achieved a class I outcome, 29 (17.0%) a class II outcome, 11 (6.4%) a class III outcome, and 7 (4.1%) a class IV outcome. 59 (34.5%) patients discontinued antiepileptic drugs and did not experience seizure recurrence for more than 2 years (Fig. 1B).

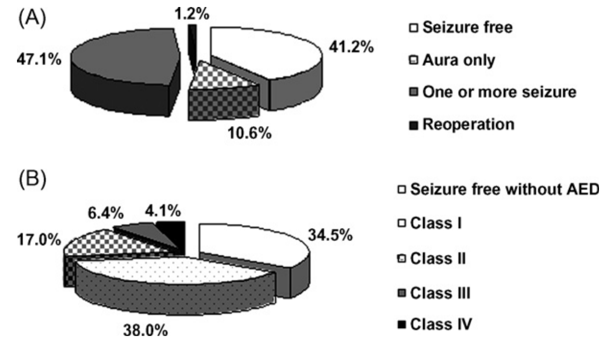

Figure 1 Seizure outcomes: (A) seizure outcome throughout postoperative follow-up period, and (B) seizure outcome for last 1 year by Engel's classification.

AEDs were tapered in 124 and discontinued in 79 seizure- and aura-free patients. 50 of these 124 (40.3%) patients experienced seizure recurrence for mean follow-up period of 40.1 ± 33.0 months since initial AED reduction. After AED discontinuation, seizures recurred in 15 of the 79 (19.0%) patients for mean follow-up period of 49.6 ± 29.9 months. Of these 15 patients, one patient later achieved a seizure free state for 44 months after re-discontinuing AEDs and six achieved a seizure-free outcome after reintroducing AEDs. Of the remaining eight, five achieved an outcome of Engel class II, two class III, and one class IV at final assessment.

Mean time to initial AED reduction after surgery was 7.76 ± 6.42 (mean $\pm$ S.D.) months, and mean time to discontinuation was 22.8 ± 13.8 months.

Table 1 Clinical characteristics of the patients

Age (year)	29.0 ± 8.63 (S.D.)
≥ 30	42.1%
<30	57.9%
Duration of epilepsy (year)	15.4 ± 8.63 (S.D.)
≥ 20	26.9%
<20	73.1%
Seizure frequency (/month)	7.51 ± 16.9 (S.D.)
History of febrile convulsions	58.0%
Number of AEDs	1 = 15.8%
	2 = 52.6%
	$3 \geq 31.6\%$
MRI	Hippocampal sclerosis: 163 (95.3%)
	Other lesions: 8 (4.7%)
Pathology	Hippocampal sclerosis
	Others: 2 CA, 3 DNET, 2 GGL, 1 Choroid plexus papilloma

CA: cavernous angioma, DNET: dysembryoplastic neuroepithelial tumor, and GGL: ganglioglioma.

Time of recurrence

First recurrences occurred during the postoperative hospitalization period in 23 (23.2%) patients, during the first postoperative year in 44 (44.4%), the second year in 14 (14.1%), the third year in seven (7.1%), the fourth year in one (1.0%), the fifth year in five (5.1%), and after the fifth year in five (5.1%) patients (Fig. 2).

Prognostic factors associated with AED withdrawal

Univariate Cox regression analysis was used to evaluate risk factors of recurrence. Patients older than 30 tended to develop recurrences ($p = 0.078$). Preoperative duration of epilepsy, seizure frequency, a history of febrile convulsions, and

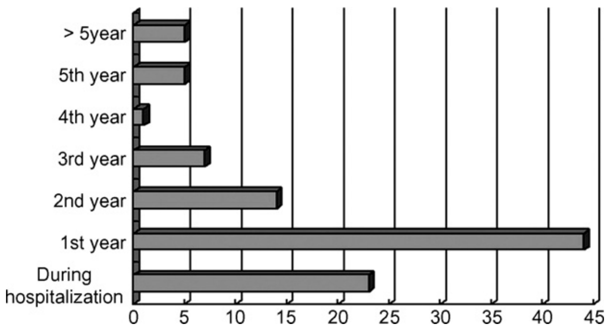

Figure 2 Time to first recurrence.

number of medications were not found to predict outcome. Hippocampal sclerosis or other pathologies did not affect the outcome. Contralateral interictal spikes were present in 26.3% of patients preoperatively but were not found to be associated with recurrence after AED withdrawal. Ictal SPECT falsely localized lesions to the contralateral side in nine (8.11%) patients, and seven of these had no relapse. PET showed reduced uptake in the contralateral side in four (2.5%) patients. Of these four, one patient discontinued AEDs without recurrence, whereas the other three developed seizure recurrence after AED tapering/discontinuation, with final outcomes of Ia, III, IV. In terms of time between surgery and AED withdrawal, AED tapering before 10 months had lapsed after surgery tended to evoke recurrence ($p = 0.075$), but the time to AED discontinuation did not (Table 2). AED tapering before or after other time points had no statistically meaningful effect.

Because time to AED tapering was possibly affected by the number of AEDs administered, we put two potential risk factors from the univariate analysis (age at surgery, time to decreasing AED) and the number of AEDs to multivariate Cox regression analysis. An age greater than 30 years at surgery and AEDs tapering before 10 months postoperatively were found to significantly increase the risk of recurrence ($p = 0.018$ and 0.031) with respective hazard ratios of 2.11 (95% CI 1.1—3.9) and 2.51 (95% CI 1.1—5.8) (Table 3 and Fig. 3). No significant differences in terms of recurrence were observed when other time points were examined. Time to AED discontinuation was not found to be a risk factor of recurrence also in multivariate analysis.

AED tapering before postoperative10 months did not significantly affect outcome at final follow-ups (Chi-square, $p = 0.347$) or 5-year postoperative outcomes (Chi-square, $p = 0.450$), and neither did it affect final success after AED discontinuation (Chi-square, $p = 0.503$)

Table 2 Factors predicting recurrence after AED withdrawal, univariate analysis

Variable	*P* value	HR	95% CI
Age ≥30 years	0.078	1.714	0.942—3.119
Duration of epilepsy ≥20 years	0.678	0.868	0.446—1.692
Seizure frequency	0.819	0.996	0.964—1.029
History of febrile convulsions	0.863	1.055	0.575—1.934
AED = 1 (reference)			
AED = 2	0.414	1.447	0.65—1.82
AED ≥ 3	0.566	0.743	0.34—1.11
MRI hippocampal sclerosis	0.914	0.925	0.223—3.830
EEG—contralateral interictal spike	0.777	1.109	0.541—2.276
Ictal SPECT—contralateral localization	0.332	0.491	0.116—2.069
PET—contralateral localization	0.666	1.368	0.33—5.73
Time to decreasing <10 m	0.075	2.988	0.894—9.986
Time to discontinuation <24 m	0.312	0.480	0.115—1.993

Table 3 Factors predicting recurrence after AED withdrawal, multivariate analysis

Variable	*P* value	Hazard ratio	95% Confidence interval
Age >30 years	0.018	2.111	1.139—3.911
Time to decreasing AED < 10 m	0.031	2.512	1.055—5.801
Number of preoperative AEDs			
AED = 1 (reference)			
AED = 2	0.425	1.450	0.582—3.610
AED ≥ 3	0.171	0.405	0.215—1.712

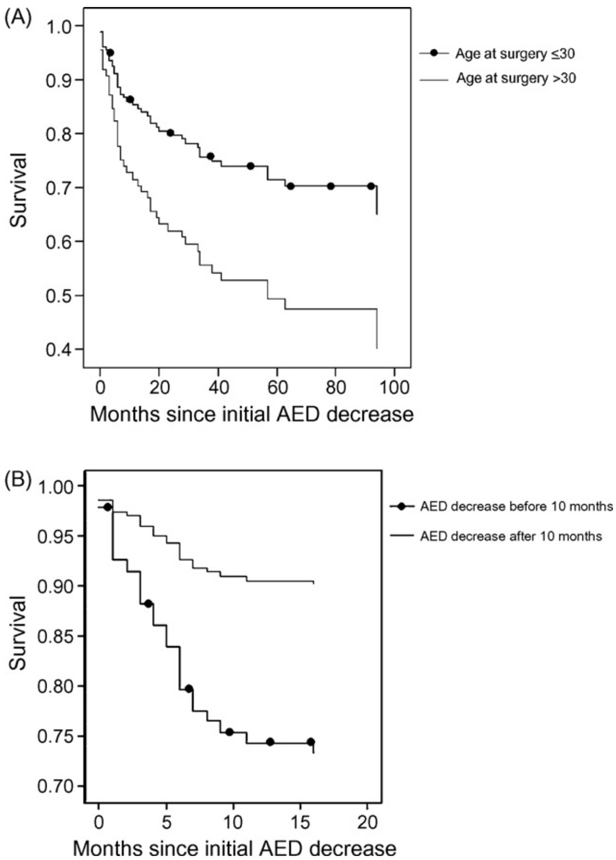

Figure 3 Survival curves according to risk factors of recurrence: (A) age at surgery. An age >30 years increased the risk of recurrence [HR 2.11 (95% CI 1.1—3.9)], and (B) the effect of time to AED tapering on recurrence. AED tapering before 10 months postoperatively increased the risk of recurrence [HR 2.51 (95% CI 1.1—5.8)].

Success of AED withdrawal after seizure recurrence

Among the patients with aura or rare seizures after surgery, AED tapering was attempted in 45 patients and AED discontinuation in 33. Of the 33, 14 (42.4%) patients achieved a seizure-free outcome over a follow up of at least 2 years.

Twenty-eight of the 45 patients experienced aura or seizure before initial AED reduction (Table 4). Recurrences in these 28 patients occurred at 0—14 months postoperatively (mean 1.96 months). All except two patients had aura or a single seizure before AED withdrawal, and all seizures were unprovoked. Of the 15 patients who experienced aura only, six successfully discontinued AEDs eventually, and these six included one patient with persistent aura but no seizure without AEDs for more than 2 years. For 13 patients who experienced seizure recurrence, AED tapering was attempted after a seizure-free period. Two of these patients succeeded in discontinuing AEDs. Two patients who had several seizures have been seizure-free for the AED reduction period more than 2 years.

We attempted to identify factors that affected AED withdrawal success after seizure recurrence unrelated with AED withdrawal, but failed to identify any prognostic factor among; time to recurrence, interval between recurrence and AED reduction, age, duration of epilepsy, number of AEDs, seizure frequency, febrile convulsions, hippocampal sclerosis, PET and SPECT findings, and the presence of interictal spikes. AED discontinuation success rates were not different for patients who experienced a seizure during the immediate postoperative period and those with later onset seizures.

We reattempted AED reduction after a seizure-free period in 17 patients who had been seizure free initially but who developed recurrence (aura in 4 and seizure in 13) after AED reduction. Seven of these patients have maintained a seizure-free state for more than 2 years since AED discontinuation (Table 4).

Discussion

AED withdrawal has been extensively studied in medically treated patients. The Medical Research

Table 4 Final outcome by Engel classification after AED withdrawal despite aura or seizure recurrence

	Aura before AED change (N = 15)	Seizure before AED change (N = 13)	Aura after decreasing AED → retry of decreasing AED (N = 4)	Seizure after decreasing AED → retry of decreasing AED (N = 13)
Ia without AED (>2 year)	5	2	1	6
Ib without AED (>2 year)	1		1	
Ia with AED	3	4		4
Ib with AED	4	2		1
II without AED		1		
II with AED	2	4	2	1
III with AED				1
IV with AED				1

Council Antiepileptic Drug Withdrawal Study Group (1991) performed a randomized study on AED withdrawal after a seizure-free period of more than 2 years and suggested that age, multiple AEDs, a shorter seizure-free period, and EEG during the previous year are risk factors for relapse after AED discontinuation.[9] Several other studies on medically treated patients also concluded a lower relapse rate after a longer seizure-free period.[9–11]

However, the proper time to withdraw AEDs after surgical treatment has not been extensively studied. One report concluded that postoperative seizure-free duration and seizure recurrence after AED withdrawal are unrelated. In this study, time between surgery and AED discontinuation was 2–6 years.[5] Another uncontrolled study compared AED discontinuance after a minimum seizure-free period of 2 years with AED maintenance in TLE patients, but found no significant difference between two groups in terms of recurrence. It suggested that AED discontinuation after a seizure-free period of 2 years is safe.[4] Surgically treated patients and medically treated patients differ fundamentally because the epileptogenic lesion is removed by surgery, and because the surgical procedure itself may induce seizure development. Our findings that tapering AEDs before 10 postoperative months have lapsed increases the risk of recurrence, but that time to AED discontinuation is unrelated to recurrence may be due to high recurrence rates during the early postoperative period.

Numbers of AEDs administered has two contradictory implications, i.e., it may reflect preoperative disease severity and a protective effect against recurrence during the early postoperative period, considering that preoperative medications were maintained for immediate postoperative period.

Age at surgery, has been identified as a prognostic factor in surgically treated MTLE patients by a number of previous studies.[12–14]. These studies found that epilepsy duration is unrelated to recurrence, which concurs with our findings. These observations probably reflect the progressive nature of MTLE. In the present study, 95.3% of patients had hippocampal sclerosis, which is known to have a latent period before seizure development after an early insult.[15] According to imaging studies, hippocampal sclerosis and cortical atrophy progress with age,[16,17] and a histologic analysis revealed that the type of neuronal damage depends on age.[18] Neuronal kindling and secondary epileptogenesis could explain a higher rate of recurrence after AED withdrawal in older patients.

The concordance rates of PET or ictal SPECT with epileptogenic lesions in temporal lobe epilepsy are about 88 and 77% respectively.[19] PET shows cerebral metabolism in the interictal state. PET is inadequate for ictal imaging because it takes one hour for the radiotracer to be metabolized and distributed throughout brain tissue. If radiotracer is injected during a seizure, results can be confusing. The false lateralizing rate of ictal SPECT in temporal lobe epilepsy is about 7%.[20] Ictal SPECT can show sites of secondary seizure spread depending on the timing of radiotracer injection, rather than another epileptic focus.

Two of four patients who showed contralateral decreased metabolism by PET experienced poor outcomes. Contralateral localization by ictal SPECT or presence of contralateral interictal spike was not found to affect outcome. Our results show that contralateral PET localization might be meaningful in terms of anticipating seizure recurrence after AED reduction.

The presence of interictal epileptic discharges (IEDs) in both temporal lobes appeared to increase the likelihood of seizures arising independently from either side,[21] and a review of an autopsy series of patients with temporal lobe epilepsy found that up to 90% of patients had bitemporal damage.[22] Several studies on surgical outcome in TLE have concluded that unilateral temporal epileptiform discharges are associated with a good prognosis,[13,14] but other studies failed to find that contralateral IEDs are related to surgical outcome.[23,24] In our series, because a multidisciplinary approach to epileptic focus determination using MRI, ictal EEG, PET and ictal SPECT might exclude multifocal epilepsy, the presence of IEDs is insufficient to predict residual epileptogenic foci, even when AEDs are completely withdrawn.

Hippocampal sclerosis has been reported to be unfavorable pathology with respect to surgical outcome as compared with small tumors or cavernous angiomas.[23] In the present study, comparison between pathologies was not possible because 95.3% of patients enrolled had hippocampal sclerosis.

A preoperative history of febrile convulsion was not found to be related to AED discontinuation related outcome, which is consistent with the findings of other studies.

Seizure recurrence mechanisms can be explained by residual epileptogenic lesions and surgery-related epileptogenicity. Surgically treated patients commonly experience seizures during the first few months or years, but these finally remit. Rasmussen described this as a "running-down phenomenon" and postulated that the hard-core, lowest-threshold, epileptogenic area is removed at surgery, and that minimal residual epileptogenic tissues are insufficient to generate seizures indefinitely.[13] In addition, it is generally believed that epileptic seizures that occur during the early postoperative period, like those that follow trauma and stroke, do not necessarily predict long-term outcome after resection,[25] although findings are conflicting. Acute postoperative seizures (APOSs) are believed to be an effect of surgical injury, and have been described as neighborhood seizures,[26] and are frequently observed after temporal lobectomy.[27] A study of frontal lobe epilepsy surgery found that APOSs during the first postoperative week were unrelated to seizure-free outcome.[28] However, studies on temporal lobe epilepsy suggest that APOS is associated with an unfavorable outcome.[26,29,30] Another study found that early postoperative recurrence, including recurrences within one week, is associated with intractability and that later recurrences were seldom intractable.[31] Most late recurrences that occur during the AED tapering period can be treatable by increasing or reintroducing AEDs, but early seizures not associated with AED tapering may not respond to AEDs. However, in terms of curability, late recurrences associated with AED tapering may indicate a less favorable outcome with respect to AED discontinuation, whereas early seizures have a chance of cure after a running-down period.

Early seizure recurrences are of three types: (1) surgical failures, i.e., due to a residual primary epileptogenic lesion; (2) those destined to run down, i.e., residual lesions with low epileptogenic potential; and (3) acute transient postoperative seizures associated with surgical injury. The differentiation of these three types is helpful for planning AED withdrawal, but such differentiations are uncertain. In the present study, AED withdrawal was performed in only 45 patients that experienced recurrence, and we were unable to identify predictors of outcome. Seizure similarity with habitual seizures has been suggested to predict persistent seizures by some[26,31] but not by others.[29] In the present study, no analysis of type of recurrent seizure was performed because outpatient interviews without video-EEG monitoring have limitations for seizure classification.

Late seizures unassociated with AED tapering are believed to be due to maturation of secondary epileptogenic lesion and resection scars.[31] In our series, three patients who were seizure-free before AED discontinuation had unfavorable outcomes despite AED reintroduction.

Final outcomes were not dependent on time to AED reduction. Early AED tapering induced more recurrences but did not affect long-term outcome or the success of AED discontinuation. This observation suggests that sufficient AEDs are needed during the early postoperative period to protect against the relatively high risk of seizure recurrence, but that early AEDs cannot prevent epileptogenesis. In spite of that, an initial AED maintenance period is required to prevent early seizures and allow observation of surgical results. Based on our results, postoperative AED tapering is recommended after at least 10 months. Longer periods until AED reduction are likely to be safer because first recurrence is not infrequent after 1 year. Further controlled study is required to determine the optimum period.

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